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ScienceDirect
Vaccine 25 (2007) 373–380
Vaccine
www.elsevier.com/locate/vaccine

Rotavirus disease in Uzbekistan: Cost-effectiveness of a new vaccine☆

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Received 30 August 2005; received in revised form 7 July 2006; accepted 19 July 2006
Available online 2 August 2006

Abstract

We evaluated the cost-effectiveness of rotavirus vaccination in Uzbekistan from the healthcare system and societal perspectives. Disease burden was estimated using national statistics on hospitalizations and deaths, and international estimates of under-five mortality. Without vaccination, the risk for rotavirus hospitalization by age 5 is 10 per 1000 children. Rotavirus hospitalizations cost US$ 406,000 annually, of which US$ 360,000 (89%) is for medical expenses and US$ 46,000 (11%) is for non-medical and indirect costs. Rotavirus mortality rate at 0.7 per 1000 derived from national data was three-fold lower than the same rate calculated from international estimates of under-five mortality. Rotavirus vaccination could reduce hospitalizations and deaths by 91% and avert US$ 370,000 in hospitalization costs alone. Vaccination would be cost-effective with vaccine prices in a range of US$ 2–25 per child. However, the cost-effectiveness is greatly influenced by mortality, vaccine price and vaccine efficacy.
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Keywords: Rotavirus; Vaccine; Cost-effectiveness

1. Introduction

Rotavirus is the most common cause of severe diarrhea among children <5 years of age, and is responsible for substantial mortality and morbidity, particularly in countries with low income [1,2]. Currently, vaccines against rotavirus are the principle strategy to reduce the disease burden worldwide [3,4], and the universal vaccination could decrease medical and societal costs of disease. While the economic impact of disease and the cost-effectiveness of vaccination have been assessed in industrialized countries [5,6], few data are available for countries with low income [7,8]. When considering an introduction of a new vaccine, national estimates of disease and economic burden and of the cost-effectiveness of vaccination are needed [9].

In the Newly Independent States of the former Soviet Union, a few studies on rotavirus disease were conducted previously [10–12] but the disease burden remains uncertain in Uzbekistan, a country in Central Asia. With a 2003 per capita gross domestic product (GDP) of US$ 389 [13], the country is eligible for funding from the Global Alliance for Vaccines and Immunization (GAVI) to purchase new vaccines. Uzbekistan already has high vaccine coverage (98%) [14] and a mature and stable infrastructure to deliver vaccines. With support from the GAVI, Uzbekistan recently introduced hepatitis B vaccine, and could be an early adopter of new rotavirus vaccines as well.

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the RVP, GAVI, or The Vaccine Fund.

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doi:10.1016/j.vaccine.2006.07.029

To facilitate decisions about the introduction of rotavirus vaccines, we conducted active surveillance for rotavirus disease in a large pediatric hospital in 2003–2004. We also performed an economic study to determine the medical and societal costs of disease in order to estimate the economic burden and project the cost-effectiveness of vaccination. Both studies were based on the World Health Organization (WHO) generic protocols [15,16], which for the first time assessed the national rotavirus disease and economic burden in a Central Asian country, eligible for international assistance for vaccine introduction.

2. Methods

2.1. Health care and societal costs

In the economic study, we collected data on healthcare costs from families of 84 children hospitalized with diarrhea in June–July 2004 at two hospitals: the Tashkent Children's Hospital, a tertiary hospital in the capital city in the east, and the Bukhara Regional Hospital, a secondary hospital in the west. Children aged 1–59 months hospitalized within 7 days of the onset of acute diarrhea, defined by the admitting physician, were eligible for enrollment. Written informed consent was obtained from parents or guardians prior to enrollment. Hospital surveillance for rotavirus was conducted in the Tashkent Hospital in 2003–2004 using the same enrollment criteria.

Data on direct medical costs of hospitalizations, i.e. the number and type of diagnostic procedures performed, the quantity of drugs and supplies used, and the length of hospital stay, were extracted from medical records of each child. Unit costs of the hospital bed day, medications, and diagnostics were obtained from national price lists and hospital invoices. Despite the free health care system, families of patients often pay fees to health care workers and purchase additional medications and supplies; these expenses were added to the direct medical costs. Data on non-medical and indirect costs were collected by trained study personnel who administered a questionnaire to parents or caregivers during face-to-face interviews. Direct non-medical costs were defined as the costs of food and transportation to and from the hospital that incurred as a result of this illness prior to and during hospitalization. Indirect or societal costs were defined as income lost by caregivers due to this illness and were calculated by multiplying the mean hourly wage reported by caregivers by the number of hours lost from paid work. All local currency costs were converted into US dollars using the 2004 exchange rate (1020 sums per US$) of the National Bank of Uzbekistan.

2.2. National disease and economic burden

To estimate the national disease and economic burden of rotavirus diarrhea, we developed a model to calculate numbers of rotavirus hospitalizations and deaths that would occur without and with vaccination for the 2004 birth cohort ($n = 538,128$) followed for first 5 years of life. The number of rotavirus hospitalizations was estimated by multiplying the number of diarrhea hospitalizations among children <5 years of age by 27%, a proportion of diarrhea hospitalizations attributable to rotavirus established in the surveillance study. Rotavirus mortality was estimated using the under-five mortality rates derived from international reports [17] and from national data submitted by the country to the WHO [18]. We then applied the 17% fraction of deaths attributable to diarrhea in countries with low-middle income [1] to estimates of under-five mortality to obtain total number of diarrhea deaths. A higher fraction of 21% estimated for countries with low income was not used because Uzbekistan has a developed healthcare system with a good access to services, and the use of a higher fraction might overestimate the true mortality. Number of rotavirus deaths was calculated by multiplying the number of diarrhea deaths in children <5 years by 20%, the fraction of diarrhea deaths attributable to rotavirus estimated previously [1]. Less severe rotavirus disease outcomes, including outpatient visits or community-based disease, were not included in the model because incidence of these outcomes was not available.

The economic burden was estimated by multiplying the mean costs per child by the expected number of cases and deaths. The health burden of rotavirus diarrhea was also estimated in terms of disability-adjusted life years (DALYs) [19]. DALYs quantify the years lost due to premature mortality and the years lived with disability, allowing for comparisons with other diseases. The DALY loss from mortality was calculated on the basis of the standardized life expectancy of 65.5 years for children less than 1-year-old in Uzbekistan. The DALY loss from all symptomatic cases was calculated on the basis of default disability weights, and an estimated duration of rotavirus illness of 6 days [20]. Estimates were discounted at a rate of 3% and weighted by age to ensure comparability [21].

2.3. Vaccine characteristics

To estimate the impact of a vaccination program on the disease burden, we combined vaccine efficacy and coverage as variable functions dependent on age. Vaccine efficacy for prevention of both rotavirus hospitalizations and deaths was 93% based upon results of clinical trials [22]. Since the vaccine will be incorporated into the current immunization schedule to coincide with the administration of the first two doses of diphtheria–tetanus toxoids–pertussis vaccine (DTP), we used the DTP-3 vaccine coverage rate of 98% at 1 year of age in Uzbekistan [14] as a proxy for rotavirus vaccination coverage. The model assumed on-time immunization of a two-dose oral vaccine at ages 2 and 4 months. Since the market price of vaccine was unknown at the time of analysis, a range of prices (US$ 2–25 per course) was used. Based on previous estimates [23–26], we assumed a low incremental cost of US$ 0.25 for oral administration of rotavirus vaccine.

Table 1
Comparison of patients enrolled in the rotavirus surveillance study and patients enrolled in the economic study in Uzbekistan, 2003–2004

Characteristics	Patients enrolled in		
	Hospital surveillance		Economic study
	No rotavirus ($n=520$) % (n)	With rotavirus ($n=196$) % (n)	($n=84$) % (n)
Age group (months)			
0–2	1 (3)	0	7 (6)
3–5	17 (87)	6 (11)	21 (18)
6–8	19 (98)	15 (29)	18 (15)
9–11	16 (81)	13 (25)	15 (13)
12–23	26 (137)	29 (57)	23 (19)
24–35	12 (65)	20 (40)	8 (7)
36–47	7 (36)	9 (18)	5 (4)
48–59	2 (13)	8 (16)	3 (2)
Sex			
Male	52 (272)	59 (115)	67 (56)
Female	48 (248)	41 (81)	33 (28)
Length of stay (days), mean (range)	6.2 (1–19)	6.8 (1–17)	6.8 (1–12)

2.4. Cost-effectiveness and sensitivity analyses

The cost-effectiveness analysis was performed from the healthcare system and societal perspectives. We calculated the incremental cost-effectiveness ratio (ICER) expressed as the cost per DALY averted and as the cost per life saved. The ICER is the net cost (costs of administering the rotavirus vaccine minus the medical costs averted by vaccination) divided by the DALYs or deaths averted by vaccination. The cost-effectiveness ratio was calculated for a range of vaccine prices. The WHO's World Health Report suggests that interventions with a ICER (in \$/DALY) of less than the per capita GDP should be considered "very cost-effective" and those with an ICER less than three times the GDP should be considered "cost-effective" [27]. We performed one-way sensitivity analyses to assess the impact of high and low estimates of rotavirus mortality and hospitalization rates, vaccine efficacy, and vaccine price on the cost-effectiveness ratios.

3. Results

3.1. Health care and societal costs

Of 84 children enrolled in the economic study, 43 (51%) were treated in the Tashkent Hospital and 41 (49%) in the Bukhara Hospital. Of the 716 children enrolled in rotavirus surveillance, 27% (196) had rotavirus detected in stools. No differences were observed between children with and without rotavirus diarrhea (Table 1). Therefore, estimates of costs incurred in treating patients enrolled in the economic study should be representative of costs incurred in treating rotavirus patients. Of the 84 patients in the economic study, 81% (68) sought medical care prior to being admitted to the hospital (Table 2). Of these 68 patients, 75% (51) attended an outpatient facility, 13% (9) visited a private physician, 4% (3) sought care in another hospital, 4% (3) went to a pharmacy, and 3% (2) visited a traditional healer. No patient received more than a single point of care prior to being admitted to the hospital. The median distance from a child's home to the hospital was 10 km (range, 1–100 km) and most caregivers (96%)

Table 2
Types of medical care sought by 84 diarrhea patients before hospitalization and sources of funds used by caregivers for out-of-pocket expenditures, Uzbekistan 2004

Variable	% (n)
Type of medical care before hospitalization	
Outpatient clinic	60 (51)
Private physician	10 (9)
Another hospital	4 (3)
Pharmacy	4 (3)
Traditional healer	3 (2)
No care	19 (16)
Means of transport to hospital[a]	
Personal car	33 (28)
Ambulance	32 (27)
Taxi	25 (21)
Public transport	11 (9)
By foot	4 (3)
Distance (km) to hospital, median (range)	10 (1–100)
Caregiver trips per day per family to hospital, mean (S.D.)	2.3 (1)
Sources of funds[b]	
Savings	73 (61)
Loan from relatives or friends	20 (17)
Reduction in other expenses	17 (14)
Sale of assets	1 (1)
Monthly household income (2004 \$), mean (S.D.)[c]	70 (44)
Children per household, median (range)	2 (1–7)
Adults per household, median (range)	4 (2–12)

[a] Four caregivers reported using more than one type of transport.
[b] Nine caregivers reported using more than one source of funds to cover out-of-pocket expenses.
[c] The 2004 exchange rate of US\$ 1.00 = 1020 Sums is applied (the National Bank of Uzbekistan, Interstate Statistical Committee of the Commonwealth of Independent States).

Table 3
Frequency and costs of diagnostic procedures in 2004 US dollars[a] incurred during hospitalizations of 84 children with acute diarrhea, Uzbekistan

Diagnostic procedures	Subjects undergoing procedures, % (n)	Procedures per subject, mean (range)	Unit cost per test, US$	Cost US$ per subject, mean (S.D.)[b],
For the child				
Blood cells count	100 (84)	1.5 (1–3)	0.37	0.60 (0.20)
Blood culture	15 (13)	1.0 (1–2)	2.50	0.42 (1.03)
Stool microscopy	100 (84)	2.3 (1–5)	0.37	0.90 (0.50)
Stool culture	99 (83)	2 (1–3)	7.50	15 (7.50)
Cholera test[c]	100 (84)	1 (1–1)	6.30	3 (0.00)
Urine test	100 (84)	1.5 (1–3)	0.32	0.50 (0.22)
HBsAg[d]	51 (43)	1 (1–2)	0.22	0.12 (0.12)
Blood protein	14 (12)	1 (1–2)	0.10	0.02 (0.04)
For the guardian[e]				
Syphilis test	51 (43)	1 (0–1)	0.45	0.23 ± 0.22
Total diagnostics cost				21 ± 7.10

[a] The 2004 exchange rate of US$ 1.00 = 1020 sums is applied (the National Bank of Uzbekistan, Interstate Statistical Committee of the Commonwealth of Independent States).
[b] Diagnostics cost = unit cost of procedure × mean number of procedures performed × proportion of children undergoing test. S.D., standard deviation.
[c] The cost of cholera test per child was adjusted because the test is performed only during 5 months of each year, i.e., from May through September.
[d] HBsAg denotes hepatitis B surface antigen.
[e] Mothers or guardians who are commonly hospitalized together with children undergo mandatory testing for syphilis per the current protocol of the Ministry of Health.

reported paying for their transportation. The main source of funds used by the families to cover costs of hospitalization was savings (73%), but others reported taking a loan from relatives or friends (20%), reducing other expenses (17%), or selling assets (1%).

The average cost of a routine diagnostic work-up for a child with diarrhea was US$ 21. The routine evaluation per current treatment protocol included a blood cell count, a chemical urinalysis, a test for hepatitis B surface antigen, at least two mandatory stool cultures for *Salmonella* and *Shigella* organisms, a latex agglutination test for cholera, and stool microscopy for blood and proteins (Table 3). In Uzbekistan, parents or guardians commonly stay in hospital together with young children and at the Tashkent Hospital, these adults also underwent obligatory testing for syphilis. Such extensive diagnostic work-ups including frequent cultures and testing for cholera (and syphilis in adults) are part of the standard protocol for infectious disease surveillance. The total average cost per hospitalized child with diarrhea was US$ 77.80 (Table 4). Direct medical costs accounted for 89% of this total, while non-medical costs constituted 10.5% and indirect costs 0.5%. Of direct medical expenses per hospitalized child, the health care system incurred 75% of the costs and the patient's family covered the remaining 25%. Only 29% of parents incurred indirect medical costs by losing time from paid work due to a child's illness.

3.2. National disease and economic burden

Based on nationally reported hospitalizations for diarrhea in children <5 years old in 2004 (n = 19,511), and on the 2004 birth cohort (n = 538,128), the estimated cumulative risk for a child to be hospitalized for diarrhea by age 5 is 36.3 per 1000 children. Since 27% of diarrhea hospitalizations in the surveillance study were attributable to rotavirus, approximately 5300 children would be hospitalized for rotavirus diarrhea annually without vaccination. Thus, the cumulative risk for hospitalization due to rotavirus disease is 10 per 1000 resulting in 1 child in every 100 being hospitalized by age 5. We estimated the annual costs of rotavirus hospitalizations to be US$ 406,358, of which US$ 361,738 (89%) are direct

Table 4
Costs in 2004 US dollars incurred in treating 84 children with acute diarrhea, Uzbekistan

Cost category	Cost per episode, mean (S.D.)
Direct medical costs	
Pre-hospitalization care[a] (medicines and physician's fee)	2.0 (4)
Diagnostics	21.0 (7)
Medicines	9.4 (29)
Bed and food[b]	21.2 (26)
Physician's fee[a]	3.2 (3)
Non-hospital medicines[a]	12.5 (15)
Total	69.3 (13)
Direct non-medical costs[a]	
Transportation	2.0 (2)
Food for caregiver	6.2 (7)
Total	8.2 (4)
Indirect costs	
Percent of caregivers who lost paid work	29
Hours of work lost, mean (S.D.)	3 (9.0)
Mean hourly wage[c]	0.40
Total	0.35
Total direct and indirect cost per episode	77.8 ± 13.5

[a] Expenses covered by caregivers.
[b] Includes a bed day cost of hospitalization ($/day) for a mean duration of 6.8 days.
[c] Mean hourly wage is calculated for a mean monthly income assuming 22 working days of 8 h/day.

Table 5
Mortality estimates in children under 5 years of age in Uzbekistan based on data from national and international reports, 2004

Events	National estimates[a]		International estimates[b]	
	Rate per 1000	No.	Rate per 1000	No.
All deaths	21	11355	68.6	36915
Diarrhea deaths	3.6	1930	12	6275
Rotavirus deaths	0.7	387	2.3	1255

[a] *Source*: World Health Organization (WHO). WHO Regional Office for Europe, Copenhagen, Denmark. European health for all database.
[b] *Source*: World Bank. World Development Indicators Online 2005.

medical costs and US$ 44,620 (11%) are non-medical and indirect costs. This does not include the costs associated with outpatient visits or home care.

In 2004, the under-five mortality rate calculated from the national data was 21 per 1000 [18], equivalent to 11,355 annual deaths. If 17% of these deaths in children <5 years are due to diarrhea, the expected diarrhea mortality rate is 3.6 per 1000 children. If rotavirus is responsible for 20% of all diarrhea deaths [1], approximately 400 rotavirus deaths would occur annually or 1 death in every 1400 children by age 5 (Table 5). However, the under-five mortality rate in 2004 estimated for Uzbekistan by the World Bank and the UNICEF [17] was 68.6 per 1000 children, equivalent to 36,915 annual deaths. By applying this rate and repeating the above calculations, we obtained 1255 rotavirus deaths annually, equivalent to 1 child in every 400 dying from rotavirus by age 5. Thus, the rotavirus mortality rate at 2.3 per 1000 derived from international estimates is three-fold greater than the same rate at 0.7 per 1000 calculated from the national data. The considerable range between the two rates is because of use of different estimates of under-five mortality, which is impossible to reconcile with currently available data.

3.3. Cost-effectiveness analysis

With the current level of routine coverage (98%) [14] and vaccine efficacy of 93% [22], an on-time rotavirus immunization program in Uzbekistan is projected to prevent annually 91% (4801) of hospitalizations in children <5 years of age. Of the total costs of rotavirus hospitalizations of US$ 406,000, the government pays ∼90% per year. By preventing hospitalizations, the vaccine program would save US$ 328,154 in direct medical expenses and an additional US$ 40,667 in direct non-medical and indirect costs (Table 6). The number of rotavirus deaths averted by vaccination would range from approximately 350 to 1150 deaths annually depending whether the mortality rate based on national data or international estimates is applied. At a vaccine price of US$ 2 per

Table 6
Estimates of rotavirus disease burden based on national data, and estimates of economic burden and cost-effectiveness of rotavirus vaccination in Uzbekistan for the 2004 birth cohort[a]

Variable	No vaccination	With vaccination	Averted by vaccination
Events			
Deaths	387 (1255)	34 (111)	353 (1144)
Hospitalizations	5268	467	4801
DALYs	12894 (41445)	1174 (3704)	11720 (37741)
Hospitalization costs, 2004 US$			
Direct medical	361738	33584	328154
Direct non-medical	42793	3791	39002
Indirect	1827	162	1665
Total	406358	37538	368820
Intervention cost, 2004 US$[b]			
Vaccination cost per course			
2	–	1423887	–
5	–	3164193	–
10	–	6064703	–
20		11865722	
Incremental cost-effectiveness ratio			
$/DALY averted, 2004 US$			
2	–	94 (29)	–
5	–	242 (75)	–
10	–	489 (152)	–
20	–	984 (306)	–
$/Life saved, 2004 US$			
2	–	3103 (958)	–
5	–	8031 (2479)	–
10	–	16245 (5015)	–
20	–	32673 (10087)	–

[a] Disease burden estimates derived from international data on under-five mortality are provided in parentheses for comparison.
[b] Intervention cost includes vaccine price and vaccine administration cost.

Table 7
Sensitivity analysis of rotavirus vaccination in Uzbekistan

Variable	Value	% Change	Cost-effectiveness ratio	% Change in ICER
Rotavirus mortality/1000				
Low	0.4	−50	971	+99
Baseline[a]	0.7		489	
High	1.1	+50	327	−33
Vaccine price per course, US$				
Low	5	−50	242	−51
Baseline	10		489	
High	15	+50	737	+51
Rotavirus hospitalizations/1000				
Low	7.3	−25	118	+1
Baseline	9.8		117	
High	12.2	+25	115	−1
Efficacy against rotavirus mortality				
Low	80	−14	135	+16
Baseline	93		117	
High	100	+8	108	−7
Efficacy against rotavirus hospitalizations				
Low	80	−14	117.4	+1
Baseline	93		116.5	
High	100	+8	116	0

[a] Rotavirus mortality rate derived from national data is the baseline.

course, a vaccination program would cost US$ 1.4 million and could avert more than US$ 328,000 in direct medical costs and US$ 41,000 in non-medical and indirect costs. Based on the World Health Report's standard for "very cost-effective" interventions [27], rotavirus vaccination would be "very cost-effective" at vaccine prices up to US$ 8 per child if the mortality rate based on national data is used. However, when another rate derived from international estimates is applied, the vaccination would be "very cost-effective" even at vaccine prices up to US$ 25 per child.

Therefore, the variability in mortality estimates and the vaccine price have the largest impact on the cost-effectiveness ratio, which is also demonstrated by the sensitivity analysis (Table 7). Raising the mortality rate calculated from the national estimates at 0.7 per 1000 by 50% provided a 33% decrease in the ICER from the baseline value, whereas lowering the rotavirus mortality rate by 50% resulted in almost 100% increase in the ICER. Vaccine prices of US$ 5 and 15 per course resulted in an ICER of US$ 242 and 737 per DALY, respectively, corresponding to a 51% change in the ICER. However, adjusting the rotavirus hospitalization rate by 25% (from 9.8 to 12.2 per 1000 children) resulted only in a 1% change in the ICER. Similarly, adjusting the vaccine efficacy against mortality had a greater impact on the ICER compared to changing the efficacy against hospitalizations.

4. Discussion

We examined costs of rotavirus diarrhea from the healthcare and societal perspectives and projected cost-effectiveness of universal rotavirus immunization in Uzbekistan. This study has quantified for the first time the disease and economic burden of rotavirus in an ex-Soviet country in Central Asia, using the limited available data on childhood hospitalizations and deaths. Without vaccination, rotavirus disease is estimated to cause 5300 hospitalizations annually in children <5 years of age. The immunization program when vaccine was delivered on schedule could prevent 91% of these hospitalizations and produce a saving of US$ 368,829 in hospitalization costs alone. The cost-effectiveness of vaccination program is greatly influenced by rotavirus mortality, followed by vaccine price and efficacy. Estimates derived in our study demonstrated a considerable range between mortality rates calculated from national and international sources of data. Since Uzbekistan has an established healthcare system with a good access to services and high vaccine coverage, the international estimates of under-five mortality might be too high. Moreover, these are generalized estimates based on extrapolations from household surveys and censuses [17], which may not be entirely representative of the country. Alternatively, the national statistics demonstrate very few under-five deaths but it probably does not reflect the true mortality either because of high under-registration of deaths and uncertainty in coding of underlying causes [18]. By comparison, the 2004 under-five mortality rate calculated from national data in Kyrgyz Republic, a country neighboring Uzbekistan, is almost two times higher than the same rate obtained from Uzbek national statistics [18]. Since two countries have similar income and healthcare systems, projections of rotavirus mortality based on the Uzbek national data may be an underestimation. The range between different estimates of under-five mortality makes difficult to examine the true burden of rotavirus disease and accurately assess the cost-effectiveness of vaccination. In fact, the difference between estimates derived from national and international reports makes us doubt the credibility of either source and emphasizes the need for reliable data on childhood mortality in low-income countries.

Nevertheless, our analysis demonstrated that rotavirus vaccination program would be cost-effective with vaccine prices in a range of US$ 2–25 per child depending on which mortality rate is applied. If estimates from national data are used, the intervention would by far less cost-effective compared to that with the use of international estimates. Universal vaccination at a vaccine price of US$ 25 per child would cost an additional US$ 15 million to the national immunization program. That said, most of vaccines used in the Expanded Program on Immunization in Uzbekistan are currently purchased at a UNICEF's average weighted price of US$ 1 per child [28]. Hence, while the US$ 25 price per course might be considered cost-effective in global economic terms, it would dramatically increase vaccine purchase costs in Uzbekistan and would not be sustainable.

Hospitalization costs in our study were mainly driven by the costs of diagnostics and the length of hospital stay. Frequent culturing and prolonged hospitalizations of patients with infectious diseases are a common practice in former

Soviet countries, resulting in inflated medical costs due to mandatory testing of patients with diarrhea for cholera, *Salmonella* and *Shigella*, and their caregivers for syphilis. If the routine work-up included only one stool culture per child and excluded tests for cholera and syphilis, the medical costs of hospitalization could be reduced by nearly 20% without any appreciable loss in quality of delivered care. Shortening the hospital stay would further decrease hospitalization costs. Thus, amending the routine diarrhea treatment protocol could be an important cost-saving strategy for a country with limited resources. However, the reduction in costs yielded by rotavirus vaccination would be greater and merely limiting unnecessary diagnostic evaluations would slightly reduce only the economic burden of rotavirus disease and have little impact on the cost-effectiveness of vaccination.

In our analysis, families of patients with diarrhea incurred one-third of total hospitalization costs and covered one-fourth of all direct medical costs by out-of-pocket expenditures. The out-of-pocket expenses represented 37% of the mean household income per month, demonstrating the substantial economic burden incurred by families. These estimates do not include costs associated with outpatient visits and likely underestimate the total burden. The introduction of routine rotavirus vaccination and use of amended diagnostic and treatment protocols might limit family-borne costs significantly.

We found low societal costs of disease because few parents reported salary loss, most of whom were women who earn less than men or traditionally stay home. Thus, our estimates may not be representative of other low-income countries where women earn income, which is a limitation of the study. Among other limitations, we used the local costs of the hospital bed day to estimate medical costs of hospitalizations. By comparison, had we used the standard WHO-CHOICE (CHOosing Interventions that are Cost Effective) project estimates for bed day costs [29] that were 28% higher, the economic burden of rotavirus hospitalization costs would be greater, making rotavirus vaccination slightly more cost-effective. However, country-specific estimates may be more precise than estimates obtained by generic methods, such as WHO-CHOICE, and therefore may be closer to the true costs. We did not include costs incurred by outpatient visits or less severe rotavirus cases because incidence rates of these outcomes and their costs were unavailable. Excluding these events that are more common but not captured by the health care system underestimates the actual disease and economic burden of rotavirus and reduces the beneficial impact of vaccination. Lastly, we assumed that implementation costs of rotavirus immunization were low, based on limited published data. If additional resources were required to introduce this new vaccine, the costs of the vaccination program would be higher.

Introducing new rotavirus vaccines in Uzbekistan could be an effective intervention because it would reduce the disease outcomes and associated health care costs. However, the ability of a country to introduce the vaccine and sustain its use will be more influenced by price than merely by cost-effectiveness estimates. To better define the disease and economic burden of rotavirus, our analysis should be expanded to include reliable estimates on childhood mortality, data on other disease outcomes, and cost estimates that reflect expenses in smaller hospitals and outpatient facilities. Similar analyses should be repeated in other countries to assess the need for new rotavirus vaccines.

Acknowledgements

We would like to acknowledge all patients, their families, and hospital staff for their assistance during the implementation of this study. *Funding sources*: This work was performed under a collaborative arrangement with the Rotavirus Vaccine Program (RVP) at PATH and was funded by the Global Alliance for Vaccines and Immunization (GAVI), and the US Centers for Disease Control and Prevention.

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